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STUDIES IN HODGKIN'S SYNDROME

I. A DISTRIBUTION STUDY OF HODGKIN'S DISEASE IN THE UNITED STATES

H. A. HOSTER

With the Technical Assistance of
F. W. SHEPARD AND L. H. HATTON¹

Although much has been said about the part played by many infectious agents in the etiology of the disease entity described by Thomas Hodgkin³ in 1832, no satisfactory statistical surveys have appeared relative to its comparative distribution in communities, states, and countries; in rural and urban populations; and in different races and climates. Information relative to the geographic and racial distribution of disease has become of increasing importance to the American physician as he himself has become migratory or as his patients may now come to him from a sojourn anywhere in the world. The possible nature of the as yet undetermined etiology of certain well established disease syndromes may be suggested by such surveys, and for this reason the present analysis was begun some two years ago as a part of an intensive study of the very considerable range of clinical and pathologic states grouped under the general designation of Hodgkin's disease. It must be said, however, that just as Thomas Hodgkin in his original report presented a series of cases, which were later recognized by careful microscopic study to comprise lymph node pathology of divergent underlying etiologies, so we, at the present time, are not certain that all of the histopathological abnormalities grouped under the heading of Hodgkin's syndrome are necessarily due to the same etiologic agent. A classification and re-emphasis of the range of clinical and histological findings observed in Hodgkin's disease has recently been presented by Jackson and Parker.⁴ It is interesting to note that, just as in similar previous analyses by other workers, there is again noted a very wide variation in both clinical and histopathological patterns grouped under the general term Hodgkin's disease; from a relatively benign "infectious" granuloma on the one hand to an invariably fatal sarcoma on the other.

The presence in Hodgkin's tissue of mycobacteria, diphtheroids, amoebae, fungi, common bacterial invaders of the upper respiratory tract, small, gram-positive, anaerobic, gas-forming rods, Brucella, and viruses has been reported in the literature. Most of the infectious agents isolated have been subsequently

¹Hodgkin's disease research carried on in the Division of Research, Department of Medicine, Ohio State University, is made possible in part by the Elise S. L'Esperance Fellowship Fund and by the Comley Research Fund.

²The maps representing the incidence of avian tuberculosis and Bang's disease in cattle are printed with the consent of the U. S. Department of Agriculture.

³Hodgkin, Thomas. "On Some Morbid Appearances of the Absorbent Glands and Spleen." *Tr. Roy. Med. Chir. Soc.*, Vol. 17, 1832, pp. 68-114.

⁴Jackson, H., Jr. and Parker, F. Jr. *New Eng. Journ. of Med.*, Vol. 230, No. 1, Jan., '44, pp. 1-8.

discarded as etiologic factors because of their failure to produce the clinical and histopathological picture of Hodgkin's disease in experimental animals, and because of conflicting and irreconcilable reports from diverse sources. Due, however, to the nature and chronicity of the clinical course, the location and granulomatous character of the lesions, and the actual demonstration of acid fast organisms in some cases, the tubercle bacillus has remained under suspicion since Sternberg's first report⁵ and has been the subject of many subsequent investigations. A few among those who have adduced direct or circumstantial evidence as to its possible causal relationship to Hodgkin's disease are Sternberg,⁵ Lichtenstein,⁶ Fraenkel and Much,⁷ L'Esperance,⁸ and Stewart and Doan.⁹ On the other hand, van Rooyan,¹⁰ Twort,¹¹ Branch,¹² Reed,¹³ Longcope,¹⁴ Terplan and Mittelbach,¹⁵ Uddstromer,¹⁶ Jackson and Parker,⁴ and others have expressed their unwillingness to accept this etiologic relationship. Classical tuberculous lesions have been demonstrated at post mortem in association with lesions typical of Hodgkin's disease in about twenty to thirty per cent of deaths attributed to the latter. When one considers conversely, however, the incidence of Hodgkin's disease in patients with proven clinical tuberculosis the correlation is found to be much lower. Medler is reported by Jackson and Parker⁴ to have found that only 0.3 per cent of a large series of tuberculous patients examined at autopsy showed the histopathological changes of Hodgkin's disease; and Uddstromer¹⁶ has reported that in Sweden the occurrence of Hodgkin's granuloma in areas where the incidence of tuberculosis is high, was actually less than in areas where the latter was low.

The suggestion made by L'Esperance that Hodgkin's syndrome may be caused by an avian tubercle bacillus⁸ or an atypical mycobacterium¹⁷ of hitherto unrecognized pathogenic importance renders a comparison of human tuberculosis with Hodgkin's disease of less significance, since the incidence of atypical infections due to strain of acid fast bacilli other than human and bovine pathogens does not follow or parallel the incidence of human pulmonary tuberculosis.

Parsons and Poston¹⁸ and Forbus¹⁹ have recently reported the isolation of organisms of the *Brucella* group from patients with typical Hodgkin's lesions, but no convincing confirmation of their very interesting and suggestive observations has as yet been published.

The incidence of Hodgkin's disease among all post mortem examinations done at general hospitals is given by Symmers²⁰ as 0.16%; Barron,²¹ 0.32%; Ciechanowski,²² 0.33%; and Jackson and Parker,⁴ 0.25%.

⁵Sternberg, C. *Ztschr. f. Heilk.* 19: 21, 1898.

⁶Lichtenstein, A. *Frankfurt Ztschr. f. Path.* 24: 29, 1921.

⁷Fraenkel, E., and Much, H. *Ztschr. f. Hug. u. Infekt.* 67: 159-200, 1910; 99: 391, 1923.

⁸L'Esperance, E. S. *J. Immunol.* 16: 27-36, Jan., 1929; 16: 37-60, Jan., 1929.

⁹Stewart, F. W., and Doan, C. A. *Annals of Surg.*, p. 141-52, 1931.

¹⁰van Rooyen, C. E. *Brit. Med. Jour.* 1: 50-51, Jan. 14, 1933.

¹¹Twort, C. C. *Journal Path. and Bact.*, Vol. 33: 539-546, July, 1930.

¹²Branch, A. *Arch. Path.* 12: 253-274, August, 1931.

¹³Reed, D. M. *J. H. H. Rep.* 10: 133, 1902.

¹⁴Longcope, W. T. *Bull. Ayer Clin. Lab. Penn. Hosp.* 1:1, 1903.

¹⁵Terplan, K., and Mittelbach, M. *Virchows Arch. f. Path. Anat.* 271: 759-866, 1929.

¹⁶Uddstromer, M. *Acta. Tuberc. Scandinav.*, supp. 1, pp. 1-225, 1934.

¹⁷L'Esperance, E. S. *Personal Communication.*

¹⁸Parsons, P. B., and Poston, N. A. *South Med. Jour.* 32: 7-13, Jan., 1939.

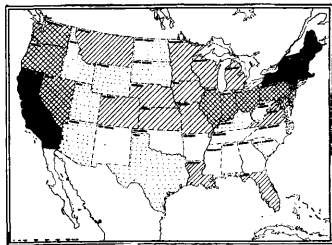
¹⁹Forbus, W. D., and Gunter, J. U. *South Med. Jour.* 34: 376, 1941.

Forbus, W. D. *Am. J. Path.*, Vol. 18, No. 4, July, 1942.

²⁰Symmers, D. *Arch. Int. Med.* 4: 218, 1909; *Arch. Int. Med.* 21:237, Feb., 1918; *Am. J. Med. Sci.* 167: 313-339, March, 1924; *Am. J. Med. Sc.* 174: 9-29, July, 1927.

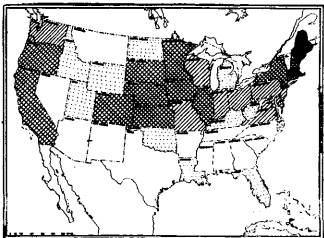
²¹Barron, M. *Arch. Path and Lab. Med.* 2: 659-690, Nov., 1926; *J. A. M. A.* 87: 1445, 1926.

²²Ciechanowski, S. *Virchows Arch. f. Path. Anat.* 303: 206-222, 1938.



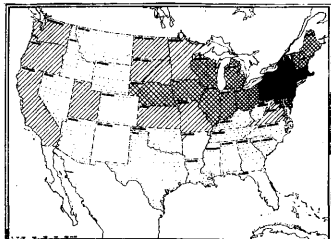
DISEASES OF THE HEART (100-00)

125-185
185-245
245-305
305-365
365-425



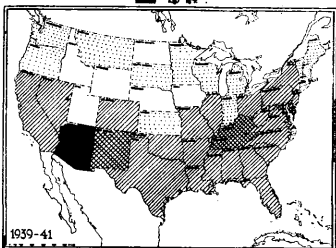
HODGKINS DISEASE MORTALITY

4-8
8-12
12-16
16-20
20-24



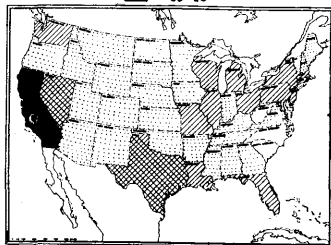
DIABETES MELLITUS (60)

5-12
12-19
19-26
26-33
33-40



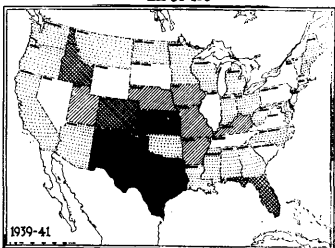
TUBERCULOSIS CASE MORTALITY

10-20 per 100,000
20-40
40-60
60-80
80-100 +



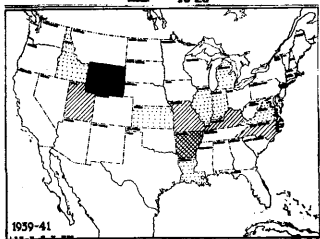
CIRRHOSIS OF THE LIVER (136)

0-4
4-8
8-12
12-16
16-20



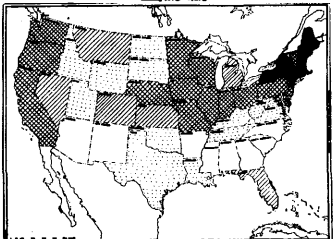
BRUCELLOSIS CASE MORTALITY

0.0-0.5 per 100,000
0.5-1.0
1.0-1.5
1.5-2.0
2.0-2.5



TULAREMIA
MORTALITY PER 100,000

0.00-0.25
0.25-0.50
0.50-0.75
0.75-1.00
1.00-1.25+



CANCER AND OTHER MALIGNANT TUMORS

50-75
75-100
100-125
125-150
150-175

METHODS

All the data concerning mortality between the years 1939 and 1941 presented in the accompanying charts (Plates I and II) were furnished by Dr. Halbert L. Dunn, Chief Statistician for Vital Statistics, Bureau of Census, Washington, D. C. No data previous to the year 1939 were used because of the revision in the International List of Causes of Death in respect to Hodgkin's Disease during the preceding year. "In 1938 the International List was revised and, effective in 1939 and thereafter, the conditions accepted for tabulation as Hodgkin's Disease were narrowed down to include only Hodgkin's Disease, Lymphatic Anemia, Lymphogranuloma, Lymphogranulomatosis, Pseudoleukemia (only when mentioned in connection with Hodgkin's disease)."²³

Statistics concerning the incidence of brucellosis and avian tuberculosis in animals (Pl. III) were obtained from the U. S. Department of Agriculture. The data representing mortality per hundred thousand in each disease entity were treated in two ways:

1. Maps (Pl. I) were compiled showing distribution by means of five gradations of the degree of positive incidence, represented by pure white, stippled, single cross hatch, double cross hatch, and solid black in order of increasing magnitude.

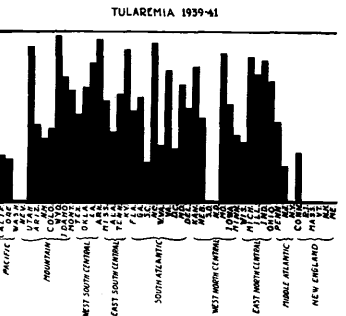
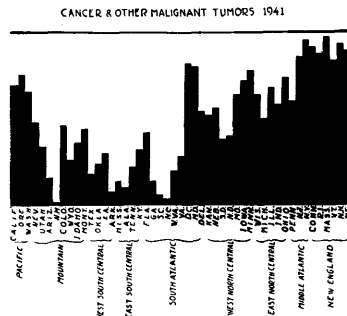
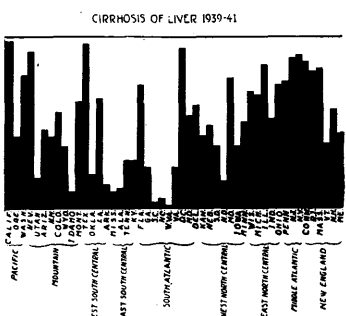
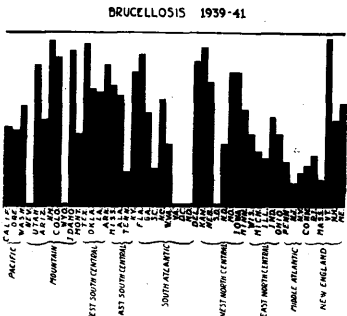
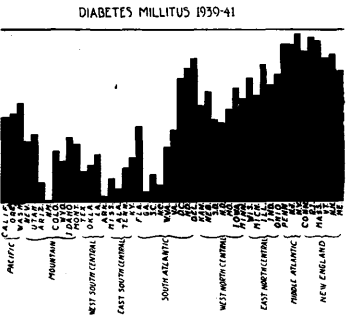
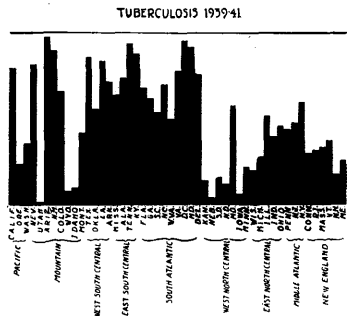
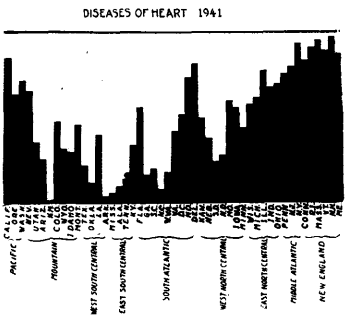
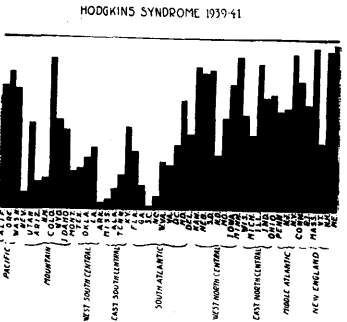
2. Another series of companion charts (Pl. II) were compiled using bars of forty-nine lengths to represent the relative order of magnitude of each state among its sister states and the District of Columbia. All states with a zero mortality in a given map are represented as first in order of increasing frequency. Similar statistics for heart disease, diabetes, cirrhosis of the liver, cancer, and other malignant tumors, and tularemia were selected for comparison and contrast.

RESULTS

A consideration of the data available for Hodgkin's disease (Pls. I and II) reveals that its greatest reported mortality is in the state of Maine. The coastal and north central states show a rather high mortality, the actual number of cases reported in the northern half of the United States being almost twice that observed in the southern half. The distribution of human tuberculosis (Pls. I and II) is entirely dissimilar; in fact, the general areas in which tuberculosis mortality is greatest are areas in which Hodgkin's disease is reported least often. The distribution of avian tuberculosis in fowl (U. S. D. A., 1931) (Pl. III) seems to be only remotely similar to Hodgkin's disease. A map issued by the U. S. D. A. in 1941 (Pl. III) is even less suggestive. The distribution of brucellosis mortality in man (Pls. I and II) is very unlike that of Hodgkin's disease; and consideration of the incidence of Bang's disease in cattle (U. S. D. A., 1941) (Pl. III) reveals no parallel to human brucellosis mortality or to Hodgkin's disease. A comparison of the population ratio of white versus other races (Pl. III) to Hodgkin's disease, diabetes, mellitus, heart disease, and neoplastic disease (Pls. I and II) reveals some similarity. The control maps, with the possible exception of cirrhosis of the liver and tularemia, bear an apparent resemblance to themselves and to Hodgkin's disease.

In a study of this type it is appreciated that there are many sources of error. A few of these may be stated as follows: differences in economic level; in population ratio of white versus other races; in medical acumen, in opinion as to diagnostic criteria, in availability of diagnostic facilities, and in migration across state borders.

²³Dunn, Halbert L. Personal Communication.



DISCUSSION

Among those diseases selected for study, the dispersion of Hodgkin's mortality data seems to resemble more closely those entities belonging to the so-called degenerative, metabolic, and constitutional inheritance groups. The inclusion of malignancy does not in our opinion necessarily constitute evidence in favor of a neoplastic etiology for all Hodgkin's disease. It is the opinion of the majority of students of the subject that Hodgkin's granuloma appears to be a non-malignant process, probably of infectious origin, and this concept is shared by us. A consideration of our own clinical material and a review of the literature points to the suggestion that Hodgkin's syndrome may result from the activity of one or more co-active infectious agents of more or less general distribution, and that definite localizing or precipitating factors such as allergy, non-specific infection, injury, constitutional and endocrine factors may be concerned in the development of the lesion. The claim for malignancy in Hodgkin's syndrome hinges on many equivocal points, namely, that the Sternberg-Reed cell is a neoplastic cell seen only in the presence of the Hodgkin's process, that invasiveness is a quality of malignancy, that the progressive character of the disease suggests malignancy, and that since the disease has not been reproduced in an experimental animal, it is not caused by an infectious agent or agents. A careful consideration of the clinical and histological picture of Hodgkin's granuloma is the most convincing evidence of the tenuous nature of these claims. A few of the arguments which militate against a neoplastic etiology are the pleomorphic character of the cellular lesions, the abundance of scar tissue formation which frequently replaces the original cellular reaction, the peculiar relapsing type of fever and tachycardia, the relative frequency of initial adenopathy in the cervical region, and the frequent spontaneous disappearances of enlarged lymph nodes without any form of therapy.

A consideration of the combined age distribution data of individuals with Hodgkin's granuloma observed by Jackson and Parker,⁴ Uddstromer,¹⁴ and ourselves²⁴ reveals the fact that the onset of "granulomatous" Hodgkin's disease occurs with a somewhat similar frequency at all ages. There is a moderate rise from the first to the third decade and an even less pronounced fall thereafter to the seventh decade. The sarcomatous type, however, is seen very infrequently before the age of twenty, and occurs with greatest frequency between the ages of fifty and seventy. It is felt that a clinical and pathological disease syndrome such as Hodgkin's granuloma with a frequency distribution extending throughout the life span should not be considered in the same etiological group with presumably neoplastic disease syndromes such as Hodgkin's sarcoma.

SUMMARY AND CONCLUSION

The dispersion pattern of Hodgkin's disease mortality is compared with the mortality of human tuberculosis and brucellosis and the incidence of fowl tuberculosis and bovine brucellosis. Certain unrelated diseases of diverse etiology are reviewed for comparison.

The fact that the majority of available evidence in the case of Hodgkin's disease favors an infectious etiology is re-emphasized.

²⁴Hoster, H. A. Unpublished data.

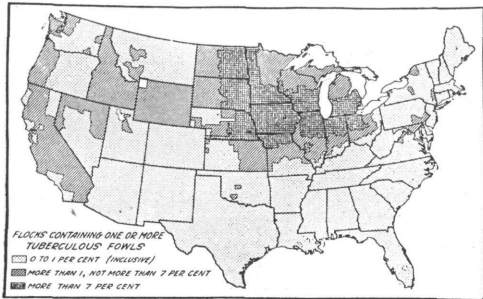


FIGURE 1.—Approximate extent of avian tuberculosis in the United States.

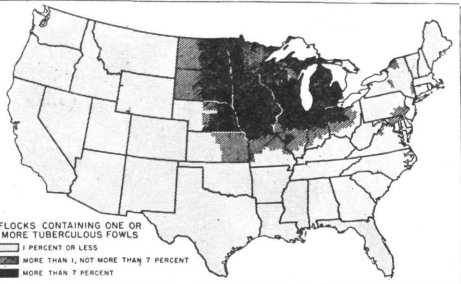


FIGURE 3.—Approximate extent of avian tuberculosis in the United States on January 1, 1941.

AVIAN TUBERCULOSIS
1931

AVIAN TUBERCULOSIS

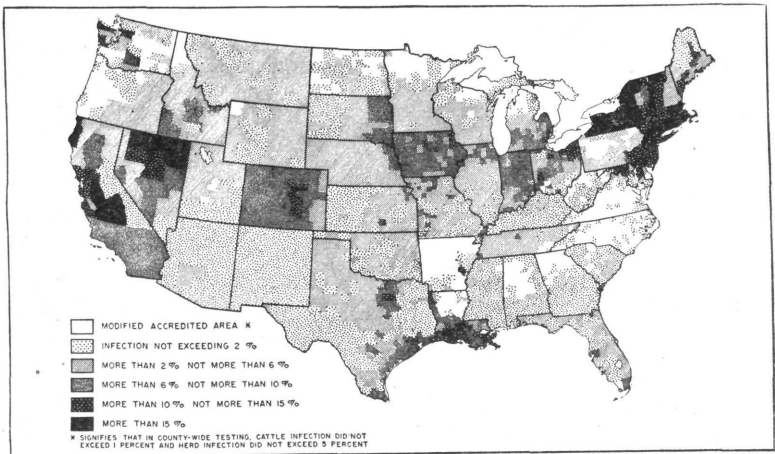


FIGURE 2.—“Modified accredited Bang’s disease-free areas” and the estimated extent of infection in the remaining counties, November 1, 1941.

BANGS DISEASE IN CATTLE, 1941
(Brucellosis)

